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(54) ANTIPHLOGISTIC AND ANALGESIC EXTERNAL PREPARATION

(57)Abstract:

PURPOSE: To obtain an antiphlogistic and analgesic agent, excellent in percutaneous absorbability of a pharmacodynamically effective ingredient and good in safety and stability.

CONSTITUTION: The objective external preparation is obtained by blending a nonsteroidal and/or a steroidal antiphlogistic and analgesic medicine as a pharmacodynamically effective ingredient and a liquid fat selected from liquid triglycerides, liquid fatty acid esters and liquid hydrocarbons and a solid fat selected from solid triglycerides, solid fatty acid esters and solid hydrocarbons as a base ingredient with an external preparation.

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CLAIMS

[Claim(s)]
[Claim 1] Resolution painkilling external preparations which contain 70% of the weight or more of liquid fat and solid-state fat to the external-preparations whole quantity as a non-steroid system and/or a steroid system resolution analgesic object, and a basis component as a drug effect component.
[Claim 2] Resolution painkilling external preparations according to claim 1 characterized by choosing said non-steroid system resolution analgesic object from the group which consists of indomethacin, a methyl salicylate, a salicylic-acid glycol, diclofenac sodium, flufenamic acid, bufexamac, ibuprofen, zaltoprofen, naproxen, flurbiprofen, flurbiprofen axetil, fenbufen, mefenamic acid, piroxicam, ampiroxicam, RISHIPUFEN, tenoxicam, felbinac, and Olcenon.
[Claim 3] Resolution painkilling external preparations according to claim 1 characterized by choosing said steroid system resolution analgesic object from the group which consists of hydrocortisone, prednisolone, methylprednisolone, betamethasone, dexamethasone, triamcinolone, triamcinolone acetonide, the flumethasone, fluocinonide, beclometasone, fluocinolone, full DOKISHIKORUCHIDO, MOMETAZON, clobetasone, clobetasol and the ester of these steroids, ketal, an acetal, and a hemiacetal derivative.
[Claim 4] Resolution painkilling external preparations according to claim 1 with which said liquid fat is characterized by being chosen more than out of a kind of triglyceride, fatty acid ester, and a hydrocarbon.
[Claim 5] Resolution painkilling external preparations according to claim 1 with which said solid-state fat is characterized by being chosen more than out of a kind of triglyceride, fatty acid ester, and a hydrocarbon.
[Claim 6] Resolution painkilling external preparations according to claim 1 characterized by the non-steroid system and/or 0.001 - 5 % of the weight of steroid system resolution analgesic objects, and containing 5 - 80 % of the weight of fatty acid ester, 5 - 70 % of the weight of triglyceride, and 5 - 60 % of the weight of hydrocarbons as a basis component as a drug effect component.
[Claim 7] Resolution painkilling external preparations according to claim 1 characterized by being the oil mixture with which the oil phase of a medicine for external application makes a continuous phase.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the resolution painkilling external preparations which contain a non-steroid system and/or a steroid system resolution analgesic object as a drug effect component in detail about resolution painkilling external preparations.
[0002]
[Description of the Prior Art] There are an aquosity gel ointment, a solution agent, cream pharmaceuticals, a tape, etc. in the non-steroid system resolution painkilling external preparations (what contains non-steroid system resolution analgesic objects, such as indomethacin and ketoprofen, as a drug effect component) and steroid system resolution painkilling external preparations (thing containing steroid system resolution analgesic objects, such as hydrocortisone acetate and prednisolone) by which current marketing is carried out. It is used from the advantage of [in a tape] gradual-release-izing of a drug from the goodness of the feel which the goodness of the usability and simple nature to cream pharmaceuticals accompanied [moisturization] in the solution agent.
[0003] Also in it, since percutaneous absorption is excellent, especially the gel ointment is widely used as a pharmaceutical form of a non-steroid system and steroid system resolution painkilling external preparations.
[0004]
[Problem(s) to be Solved by the Invention] However, since the above gel ointments contain a lot of lower alcohol (ethanol, isopropanol, etc.) and polyhydric alcohol (propylene glycol, a polyethylene glycol 300, polyethylene glycol 400, etc.) as an indispensable component for the purpose of improvement in the solubility of the non-steroid system resolution analgesic object which is a drug effect component, or a steroid system resolution analgesic object, and percutaneous absorption, they have a problem from the safety side of stimulative [over the skin].
[0005] Moreover, when this gel ointment is applied to the skin, in order not to take a means to usually seal a spreading side, the lower alcohol in a basis vaporizes immediately, and has the problem that the crystal of a drug effect component ****, and, as a result, also has the problem that the percutaneous absorption of a drug effect component is barred.
[0006] On the other hand, research which aimed at the improvement in percutaneous absorption of a drug effect component by combination of penetration enhancer is also done. As penetration enhancer, dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), etc. are known. However, since addition of a lot of penetration enhancer is the need in order to make an effective target do percutaneous absorption of the drug effect component, the present condition is not being said to be what there is a problem from safety sides, such as stimulative [over the skin of penetration enhancer], and can be satisfied in a percutaneous absorption facilitatory effect like said alcohols, and having not yet resulted in utilization.
[0007]
[Means for Solving the Problem] In the above situations, this invention persons completed header this invention for the resolution painkilling external preparations excellent in percutaneous absorption,

safety, and stability being obtained, when forming the pharmaceutical form which a specific basis component is blended with a resolution analgesic object, and an oil phase becomes from the oil mixture of a continuous phase as a result of examining many things, in order to solve the above-mentioned trouble.

[0008] Namely, this invention, A non-steroid system and/or a steroid system resolution analgesic object, and the resolution painkilling external preparations that contain 70% of the weight or more of liquid fat and solid-state fat to the external-preparations whole quantity as a basis component are offered as a drug effect component.

[0009] As a resolution analgesic object used for the external preparations of this invention as a drug effect component, indomethacin, a methyl salicylate, a salicylic-acid glycol, diclofenac sodium, flufenamic acid, bufexamac, ibuprofen, zaltoprofen, naproxen, flurbiprofen, flurbiprofen axetil, fenbufen, mefenamic acid, piroxicam, ampiroxicam, RISHIPUFEN, tenoxicam, felbinac, Olcenon, etc. are mentioned by the thing of a non-steroid system.

[0010] Moreover, in the thing of a steroid system, hydrocortisone, prednisolone, methylprednisolone, betamethasone, dexamethasone, triamcinolone, triamcinolone acetonide, the flumethasone, fluocinonide, beclometasone, fluocinolone, FURUOME TRON, full DOKISHIKORUCHIDO, MOMETAZON, clobetasone, clobetasol and the ester (betamethasone butyrate propionate etc.) of these steroids, ketal, an acetal, a hemiacetal derivative, etc. are mentioned.

[0011] As liquid fat used for the external preparations of this invention as a basis component, there are triglyceride, liquefied fatty acid ester, a liquefied hydrocarbon, etc., and there are solid triglyceride, solid fatty acid ester, a solid hydrocarbon, etc. as solid-state fat.

[0012] Although saturated fatty acid (C8-C19) triglyceride, unsaturated fatty acid (C8-C19) triglyceride, straight-chain-fatty-acid (C8-C19) triglyceride, branched chain fatty acid (C8-C19) triglyceride, etc. are mentioned, if the triglyceride as liquid fat is used for the external preparations for physic, or the charge of makeup, it is satisfactory.

[0013] As for the fatty acid ester as liquid fat, myristic-acid isopropyl, a palmitic-acid isopropanal building, butyl stearate, lauric-acid hexyl, myristic-acid octyldodecyl, oleic acid oleyl, dimethyl octanoic-acid hexyl DESHIRU, lactic-acid Millis Chill, a diethyl phthalate, phthalic-acid JIPUCHIRU, etc. are mentioned.

[0014] As for the hydrocarbon as liquid fat, a liquid paraffin, squalene, squalane, pristane, etc. are mentioned. As for the triglyceride as solid-state fat, cacao butter, palm fat, palm kernel oil, Japan wax, palm oil, beef tallow, lard, hardened oil, hydrogenated castor oil, lanolin fatty-acid triglyceride, etc. are mentioned.

[0015] As for the fatty acid ester as solid-state fat, yellow bees wax, a carnauba wax, spermaceti wax, lanolin, hydrogenation lanolin, hard lanolin, candelilla wax, etc. are mentioned. Although vaseline, paraffin, an ozokerite, a ceresin, a micro crystallin wax, polyethylene powder, etc. are mentioned, if the hydrocarbon as solid-state fat is used for the external preparations for physic, or the charge of makeup, it is satisfactory.

[0016] The resolution painkilling external preparations of this invention are fundamentally manufactured by blending one or more sorts of the one or more sorts and solid-state fat of a resolution analgesic object, and one or more sorts of liquid fat. Here, although the loadings of a resolution analgesic object change with the classes, it is desirable that it is generally 0.001 - 5 % of the weight (it is only hereafter described as "%") to the external-preparations whole quantity.

[0017] Moreover, although the total quantity of liquid fat and solid-state fat changes with those classes and classes (or desirable hardness) of pharmaceutical form, generally it is 70 - 99% preferably 70% or more to the external-preparations whole quantity. These sum total loadings cannot expect the remarkable increment in the percutaneous absorption of a resolution analgesic object at less than 70%, and a desirable thing is difficult to get also in respect of stability and safety.

[0018] in addition, as loadings according to [various / in external preparations] component About triglyceride, 20 to 50% preferably 5 to 80% 5 - 70%, [fatty acid ester] Although 10 - 20% of range is preferably suitable 5 to 60% about 20 - 45%, and a hydrocarbon preferably and it changes also with

pharmaceutical forms (for example, anhydrous ointment, W/O ointment) on the other hand about the moisture content contained in external preparations, generally it is 0 - 30% of range.
[0019] In addition to said component, a moisturizer, an emulsifier, an antioxidant, antiseptics, a chelating agent, perfume, etc. can be suitably blended with the resolution painkilling external preparations of this invention if needed. As a moisturizer, polyglycerin, such as a glycerol, 1, 3-butylene glycol, propylene glycol, dipropylene glycol, ethylene glycol, 1, 4-butylene glycol, diglycerol, and triglycerol, a glucose, a maltose, maltitol, cane sugar, fructose, a sleigh toll, erythritol, amylolysis sugar, etc. are mentioned.
[0020] As an emulsifier, sorbitansesquiolate, DEHIMURUSUF, glycerol mono-olate, glycerol diolate, sorbitan mono-olate, etc. are mentioned. As an anti-oxidant, butyl-ized hydroxytoluene, butyl-ized hydroxyanisole, a tocopherol, a sodium pyrosulfite, acetone SOJIUMUBI sulfate, etc. go up.
[0021] As antiseptics, the methyl of a p-oxy-benzoic acid, ethyl, propyl, butyl ester (respectively henceforth the methylparaben, ethylparaben, propylparaben, and the butylparaben), o-phenylphenol, a dehydroacetic acid, its salt and p-cresol, m-cresol, a p-crawl-m-xylenol, etc. can be used.
[0022] As a chelating agent, EDTA (ethylene-diamine-tetraacetic acid), thioglycolic acid, thiolactic acid, a thio glycerol, etc. can be used. Moreover, it is desirable to add a citric acid, a lactic acid, a tartaric acid, etc. to the resolution painkilling external preparations of this invention, and to adjust pH. Although a ******** decision is made at the stability of pharmaceutical preparation, as for pH which should be adjusted, usually considering as neutrality thru/or the acescence is desirable.
[0023] Furthermore, it can also blend with the resolution painkilling external preparations of this invention combining the anti-sex matter, an antihistamine, a germicide, and one or more vitamins.
[0024]
[Function] The resolution painkilling external preparations of this invention are obtained as an oil mixture whose oil phase is a continuous phase by using together liquid fat and solid-state fat as a basis component. The pharmaceutical forms of the medicine for external application which consists of such an oil mixture may be any of a solution, gel, a cream, and ointment.
[0025] Moreover, a cream may be a W/O cream and ointment may be any of W/O ointment and anhydrous ointment. As gel, polyethylene-micro crystallin wax system gel is desirable.
[0026] In these pharmaceutical forms, the mixed stock of liquid fat and solid-state fat does not have the stimulus nature to the skin, either, and does not have aging, either, and contributes to the improvement in percutaneous absorption of a non-steroid system and a steroid system resolution analgesic object.
[0027]
[Example] Below, the example of this invention is explained.
[0028]
[Examples 1-4] As an example of this invention, the resolution painkilling external preparations which contain indomethacin as a drug effect component are explained.
Each component of a publication was mixed to the <process> table 1, and the resolution painkilling external preparations of oil gel were manufactured.
[0029]
[Table 1]

成　　分	実施例1	実施例2	実施例3	実施例4
脂肪酸エステル (ミリスチン酸オクチルドデシル)	5.0g	6.0g	7.0g	8.0g
トリグリセライド (ヒマシ油)	19.55g	18.55g	17.55g	16.55g
炭化水素 (マイクロクリスタリンワックス)	7.5g	7.5g	7.5g	7.5g
ラノリン	12.5g	12.5g	12.5g	12.5g
インドメタシン	0.45g	0.45g	0.45g	0.45g

[0030] On the other hand, each resolution painkilling external preparations of the shape of the shape of an O/W mold cream containing indomethacin, gel, and a solution were manufactured as an example of a comparison over this invention, and it considered as the examples 1-3 of a comparison.
[0031] (Example 1 of a comparison) The following component was mixed and O/W mold cream-like resolution painkilling external preparations were manufactured.
Polyoxyethylene (20) sorbitol monostearate 5g cetanol 5g liquid paraffin 30g methylparaben 0.2g butylparaben 0.1g indomethacin 1g purified water 58.7g [0032] (Example 2 of a comparison) The following component was mixed and gel resolution painkilling external preparations were manufactured.

Adipic-acid diisopropyl 10g propylene glycol 5g polyoxyethylene (60) sorbitol monostearate 4g high screw 14 0.2g diisopropanolamine 0.05g indomethacin 1g purified water 79.75g [0033] (Example 3 of a comparison) The following component was mixed and solution-like resolution painkilling external preparations were manufactured.
Propylene glycol 99g indomethacin 1g [0034] The percutaneous absorption of a drug effect component of the resolution painkilling external preparations of the <percutaneous absorption [of a drug effect component] test> above-mentioned example and the example of a comparison was investigated by the diffusion cel examining method. the guinea pig regions of back which carried out depilating to the skin -- extracting -- this skin -- a sink (Sink) type diffusion cel -- equipping -- a donor side -- the external preparations (specimen) of each example -- applying -- a receptor side -- the phosphate buffered saline of pH7.4 -- using -- 37-degree C constant temperature -- it carried out the quantum, having used as the amount of percutaneous absorption the amount of the indomethacin which carried out the constant-rate sampling from the receptor side in the condition, and has carried out endermic transparency with high performance chromatography at the receptor side. The rate of percutaneous absorption of 48 hours after is shown in Table 2.
[0035]
[Table 2]

	経皮吸収率（%）
実施例1	9．0
実施例2	10．2
実施例3	11．4
実施例4	8．5
比較例1	0．6
比較例2	3．0
比較例3	4．0

[0036] The resolution painkilling external preparations of this example are excellent in the effectiveness of promoting the rate of percutaneous absorption of indomethacin compared with a comparison article so that more clearly than this result.
[0037]
[Examples 5-8] Next, the resolution painkilling external preparations which contain prednisolone as a drug effect component are explained as an example of this invention.
Each component of a publication was mixed to the <process> table 3, and the resolution painkilling external preparations of oil gel were manufactured.
[0038]
[Table 3]

成　分	実施例5	実施例6	実施例7	実施例8
脂肪酸エステル (ミリスチン酸オクチルドデシル)	5.0g	6.0g	7.0g	8.0g
トリグリセライド (オリーブ油)	19.55g	18.55g	17.55g	16.55g
炭化水素 (マイクロクリスタリンワックス)	7.5g	7.5g	7.5g	7.5g
ラノリン	12.5g	12.5g	12.5g	12.5g
プレドニゾロン	0.45g	0.45g	0.45g	0.45g

[0039] On the other hand, each resolution painkilling external preparations of the shape of the shape of an O/W mold cream containing prednisolone, gel, and a solution were manufactured as an example of a comparison over this invention, and it considered as the examples 4-6 of a comparison.
[0040] (Example 4 of a comparison) The following component was mixed and O/W cream-like resolution painkilling external preparations were manufactured.
Polyoxyethylene (60) sorbitol monostearate 5 g cetanol 5 g liquid paraffin 30 g methylparaben 0.2g butylparaben 0.1g prednisolone 1 g purified water 58.7g [0041] (Example 5 of a comparison) The following component was mixed and gel resolution painkilling external preparations were manufactured.

Adipic-acid diisopropyl 10g propylene glycol 5g polyoxyethylene (60) sorbitol monostearate 4g carboxyvinyl polymer 0.2g diisopropanolamine 0.05g prednisolone 1g purified water 79.75g [0042] (Example 6 of a comparison) The following component was mixed and solution-like resolution

painkilling external preparations were manufactured.
Propylene glycol 99g prednisolone 1g [0043] The amount of percutaneous absorption of prednisolone was calculated like the <percutaneous absorption trial of drug effect component> examples 1-4. The rate of percutaneous absorption of 48 hours after is shown in Table 4.
[0044]
[Table 4]

	経皮吸収率（%）
実施例5	8．8
実施例6	11．3
実施例7	9．5
実施例8	10．6
比較例4	0．3
比較例5	2．5
比較例6	3．4

[0045] The resolution painkilling external preparations of this example are excellent in the effectiveness of promoting the rate of percutaneous absorption of prednisolone compared with a comparison article so that clearly from this result.
[0046]
[Examples 9-12] As an example of this invention, the resolution painkilling external preparations of the shape of a W/O cream containing indomethacin are explained.
The component shown in the <process> table 5 was mixed, and W/O cream-like resolution painkilling external preparations were manufactured.
[0047]
[Table 5]

成　　分	実施例9	実施例10	実施例11	実施例12
ソルビタンセスキオレート	1.5g	2.0g	2.5g	3.0g
混合乳化剤1)	2.5g	2.5g	2.5g	2.0g
脂肪酸エステル（ミリスチン酸オクチルドデシル）	30.0g	35.0g	35.0g	35.0g
炭化水素（スクワラン）	16.0g	16.0g	20.0g	20.0g
トリグリセライド（トリ-2-エチルヘキサン酸グリセリン）	25.0g	25.0g	25.0g	30.0g
インドメタシン	1.0g	1.0g	1.0g	1.0g
精製水	24.0g	19.0g	14.0g	9.0g

1）：クエン酸ジステアリルアルコールエステル：ジヤシ油脂肪酸ペンタエリスリット：モノオレイン酸グリセリン　1：1：1

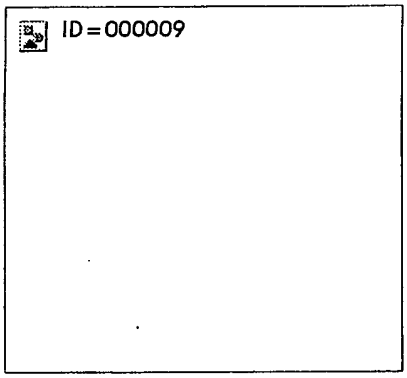
[0048] About the resolution painkilling external preparations of this example, and the resolution painkilling external preparations of the examples 1-3 of a comparison, it asked for the rate of percutaneous absorption of indomethacin like the above. A result is shown in Table 6.
[0049]
[Table 6]

	経皮吸収率（%）
実施例９	９．６
実施例１０	１０．１
実施例１１	１１．５
実施例１２	１２．９
比較例１	０．６
比較例２	３．０
比較例３	４．０

[0050] The resolution painkilling external preparations of this invention are excellent in the effectiveness of promoting the rate of percutaneous absorption of drugs, also in the shape of W/O compared with the comparison article like oil gel so that clearly from this result.
[0051]
[Examples 13-16] As an example of this invention, the resolution painkilling external preparations containing indomethacin of oil gel are explained.
Each component of a publication was mixed to the <process> table 7, and the resolution painkilling external preparations of oil gel were manufactured.
[0052]
[Table 7]

成　分	実施例１３	実施例１４	実施例１５	実施例１６
脂肪酸エステル（パルミチン酸セチル）	12.5g	15.0g	22.5g	25.0g
トリグリセライド（オリーブ油）	5.0g	5.0g	5.0g	5.0g
炭化水素（流動パラフィン）	7.5g	7.5g	7.5g	7.5g
ラノリン	19.55g	17.05g	9.55g	7.05g
インドメタシン	0.45g	0.45g	0.45g	0.45g

[0053] About the resolution painkilling external preparations of the above-mentioned example, and the resolution painkilling external preparations of the examples 1-3 of a comparison, it asked for the rate of percutaneous absorption of indomethacin like the above. A result is shown in Table 8.
[0054]
[Table 8]



[0055]
[Examples 17-20] As an example of this invention, the resolution painkilling external preparations containing prednisolone of oil gel are explained.
Each component of a publication was mixed to the <process> table 9, and the resolution painkilling external preparations of oil gel were manufactured.
[0056]
[Table 9]

成　分	実施例１７	実施例１８	実施例１９	実施例２０
脂肪酸エステル (ミリスチン酸オクチルドデシル)	10.0g	10.0g	10.0g	10.0g
炭化水素 (流動パラフィン)	10.0g	15.0g	20.0g	25.0g
ミツロウ	10.0g	10.0g	10.0g	10.0g
カルナウバロウ	14.55g	9.55g	4.55g	—
プレドニゾロン	0.45g	0.45g	0.45g	0.45g

[0057] About the resolution painkilling external preparations of the above-mentioned example, and the resolution painkilling external preparations of the examples 4-6 of a comparison, it asked for the rate of percutaneous absorption of prednisolone like the above. A result is shown in Table 10.
[0058]
[Table 10]

	経皮吸収率（%）
実施例１７	8．6
実施例１８	7．8
実施例１９	8．4
実施例２０	6．7
比較例４	0．3
比較例５	2．5
比較例６	3．4

[0059]
[Examples 21-24] As an example of this invention, the resolution painkilling external preparations containing betamethasone butyrate propionate of oil gel are explained.
Each component of a publication was mixed to the <process> table 11, and the resolution painkilling external preparations of oil gel were manufactured.
[0060]
[Table 11]

成　分	実施例２１	実施例２２	実施例２３	実施例２４
トリグリセライド（大豆油）	10.0g	15.0g	20.0g	25.0g
炭化水素（スクワラン）	5.0g	5.0g	5.0g	5.0g
ラノリン	10.0g	10.0g	10.0g	10.0g
酪酸ﾌﾟﾛﾋﾟｵﾝ酸ﾍﾞﾀﾒﾀｿﾞﾝ	19.55g	14.55g	9.55g	4.55g
ベタメタゾン	0.45g	0.45g	0.45g	0.45g

[0061] It asked for the rate of percutaneous absorption of betamethasone butyrate propionate like the above about the resolution painkilling external preparations of this example and the examples 7-9 of a comparison which transposed the indomethacin in the example 1-3 of a comparison to betamethasone butyrate propionate. A result is shown in Table 12. [0062]
[Table 12]

	経皮吸収率（%）
実施例２１	１３．５
実施例２２	１１．１
実施例２３	１０．３
実施例２４	１２．８
比較例７	0．4
比較例８	2．7
比較例９	3．6

[0063] The resolution painkilling external preparations of this invention excel [each] in the effectiveness of promoting the rate of percutaneous absorption of drugs, compared with the comparison article so that clearly from the result of Tables 8, 10, and 12.
[0064]
[Effect of the Invention] since the percutaneous absorption of the non-steroid which is a resolution analgesic object, and a steroid increases remarkably and also reinforces a bioavailability operation in the resolution painkilling external preparations of this invention by use of the liquid fat which does not have the stimulus nature to the skin as a base material component, and solid-state fat -- inflammatory diseases, such as eczema, ****, ******, ****, muscular pain, and arthritis, -- apply -- the symptom -- effective and insurance -- disappearance -- or remission can be carry out.
[0065] Moreover, in the resolution painkilling external preparations of this invention, since it is the same, in order for there to be no loss of the non-steroid and steroid which are an active principle and to carry out a distributed reservoir over long duration at the skin moreover, it excels in usability, in that the effectiveness of this non-steroid and a steroid is demonstrated effectively.
[0066] Furthermore, since moisture is 30% or less, the resolution painkilling external preparations of this invention cannot receive hydrolysis easily, and are stable with time, and there is also little change of coloring etc.

[Translation done.]